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SOME PROPERTIES OF THE TOXIN OF SHIGELLA SHIGAE AND THE EFFECT OF ADENOSINETRIPHOSPHORIC ACID ON THE TOXIC ACTION PRODUCED BY THIS TOXIN

[This report summarizes a communication from the Pharmacological Institute, Charles University, and the Institute of Epidemiology and Microbiology, of Prague, Czechoslovakia. The communication was signed by H. Raskova, B. Rybova, K. Raska, J. Jelinek, and V. Matejevska.]

In a number of previous communications we have shown that the toxin of Shigella shigae acts on the body not only by reason of its direct effect on the organs, but also because it produces a reflex irritation of interoreceptors (Raskova, and others, 1952). The problem of the action of drugs on the carotid sinus has been investigated in the USSR. This work has been summarized in a recently published article by V. S. Anichkov (1951). Starting from Anichkov's work, we established in the course of our own work (Raskova and others, 1952) that TSK (the toxin of Shigella shigae) excites the interoreceptors of the blood vessels of the intestine and in this manner brings about reflex changes in the blood pressure and respiration. Acetylcholine under normal conditions is a powerful stimulant of interoreception (Anichkov, 1951). However, TSK, while it temporarily stimulates interoreception, blocks the sensitivity of interoreceptors towards acetylcholine.

We have further shown that this blocking effect can be removed or prevented by adding ATP (adenosinetriphosphoric acid) to the perfusing liquid. It is known that ATP sensitizes interoreceptors towards acetylcholine (Belen'kiy, 1951).

In a subsequent part of our work we have shown how the sensitivity of interoreceptors towards TSK changes on repeated introduction of this toxin into the body. We found that the animals rapidly cease to respond by a stimulation of the vascular interoreception to an introduction of the toxin, while sensitivity to the action of acetylcholine is retained. After the third immunizing

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impulse, one usually observes absence of reflectory response, i.e., neither administration of acetylcholine nor introduction of TSK into the blood vessels of the intestine brings about reflex changes of the blood pressure or respiration. In an attempt to increase, during the course of the immunization process, the reactivity of the organism to TSK and to acetylcholine by introducing ATP, which on the first contact of the toxin with the organism considerably reinforces the reaction not only to acetylcholine, but also to the toxin, we obtained, in the initial stage of immunization, an increased sensitivity of the interoreceptors towards acetylcholine, but were not able to induce reflex reactions to TSK.

We have also found that the reactivity is reestablished over paradoxal reactions, i.e., there is temporary lowering of the blood pressure instead of an initial rise, and vice versa. The fact that there are paradoxal reactions was checked in experiments on nerve-muscle preparations of rabbits and cats in situ (Raskova, and others, 1952). In these experiments, we brought about by means of TSK a typical Vvedenskiy parabiosis, the dynamics of which we observed in the course of immunization. The results we obtained convinced us on the basis of data published by N. V. Golikov (1950) and A. D. Ado (1951) that TSK induces parabiotic processes in the organism. ATP, by modifying the functional lability of the interoreceptors and of the motor nerve, exerts a considerable influence on the course of the reaction induced by TSK.

The effect of ATP proved to be different at the time of the initial contact of the interoreceptors with the toxin, when ATP not only had a sensitizing effect on the acetylcholine reaction, which in this case may be regarded as a model of the regulatory impulses that normally take place in the body, but also brought about sensitization of the interoreceptors towards TSK. As distinguished from this mode of action, ATP in the initial stage of immunization did not modify the sensitivity of the interoreception to the toxin, but increased its sensitivity to acetylcholine. On the basis of what has been said above we concluded that if a two-stage action of the type described is actually exerted, administration of ATP simultaneously with the toxin must increase the toxicity of the latter. On the other hand, administration of ATP at a time when poisoning with TSK has already taken place must reduce the toxicitv of TSK. The greatest effect of ATP must take place prior to the time at which the maximum lethality of the experimental animals occurs.

Our experiments on white mice confirmed fully our working hypothesis and formed a basis for the application in therapy of the relationships that had been established. We found that depending on the changing dynamics of the pathological process which takes place in the body, the identical substance may exhibit opposite properties. It may aggravate the fundamental pathological process or alleviate it considerably. In view of the fact that we established in prior experiments that different changes take place in the interoreceptors after introduction of ATP, depending on the state of the functional lability of the interoreceptors at the time they were exposed to the action of TSK, and taking into consideration the fact that we observed directly the development of a parabiotic process after introduction of TSK, as well as the effect of ATP on this process, we conclude the ATP participates in the parabiotic process. We have seen on the example of ATP how important it is to take into consideration at the time when a therapeutic agent is administered the state of functional lability of the structures on which action is to be exerted.

This lability changes during the course of the pathological process. If a parabiotic process is induced by means of TSK, the character of the influence on the course of this process and the stage or phase of parabiosis at which this process ceases depend on the conditions which existed at the time when the substance in question was introduced. This is why the time factor is of such great importance. By selecting the right time interval, we may achieve

the result that the interoreceptor structures or other structures of the organism will exhibit a physiological lability in the direction which is of advantage to us from the therapeutic standpoint. Taking into consideration the fact that many drugs bring about development of a parabiotic process in the organism, or exert a certain influence on a process which is already present, one realizes that application of the action of drugs on the functional lability in the desired direction is a very difficult matter. One may therefore conclude that a pharmacology which is based on N. Ye. Vvedenskiy's theory may contribute much that is new to therapy.

Our experiments show that the time factor may be of substantial importance in connection with the administration of a drug during the course of a disease. If the drug is administered at the right time, it may have a beneficial effect on the course of the disease. However, administration of the drug at the wrong time may have a highly adverse effect and stimulate development of the pathological process in the wrong direction. Hitherto, this fact has not been adequately considered in pharmacology.

Our experimental results show that the toxic effect produced by TSK can be modified to a considerable extent by administering the calcium salt of ATP. The character of the results achieved depends on the time of the administration of ATP. If ATP (in a quantity of 10 mg/kg) and TSK are administered simultaneously, the toxicity of TSK is increased to a considerable extent. If ATP is administered after TSK, the toxicity of the latter is considerably reduced, reaching a minimum when ATP is introduced 30-36 hours after the administration of TSK. The experimental results obtained have been thoroughly evaluated statistically. It follows from these results that the time factor pertaining to the administration of a drug in relation to the development of the pathological process can be of substantial importance.

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